Wael S.I. Abou-Elmagd, Ahmed K. EL-Ziaty and Abdelaal A. Abdalha*

Ring transformation and antimicrobial activity of indolyl-substituted 2(3*H*)-furanones

Abstract: A variety of heterocycles of synthetic and biological importance were prepared from 3-(indol-3-ylmethylene)-5-phenyl-2(3*H*)-furanone (**1**) and its hydrazide **2**. Compounds **1** and **2** were used for the construction of pyridazin-3(4*H*)-ones **4** and **6**; 1,3,4-oxadiazoles **7**, **8**, and **10**; and 1,2,4-triazoles **12**, **14**, and **15**, all bearing a 3-indolyl moiety. The antimicrobial activities of the synthesized compounds were examined against six types of bacteria and two types of fungi.

Keywords: 2(3*H*)-furanone; indole; oxadiazole; pyridazinone; triazole.

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Introduction

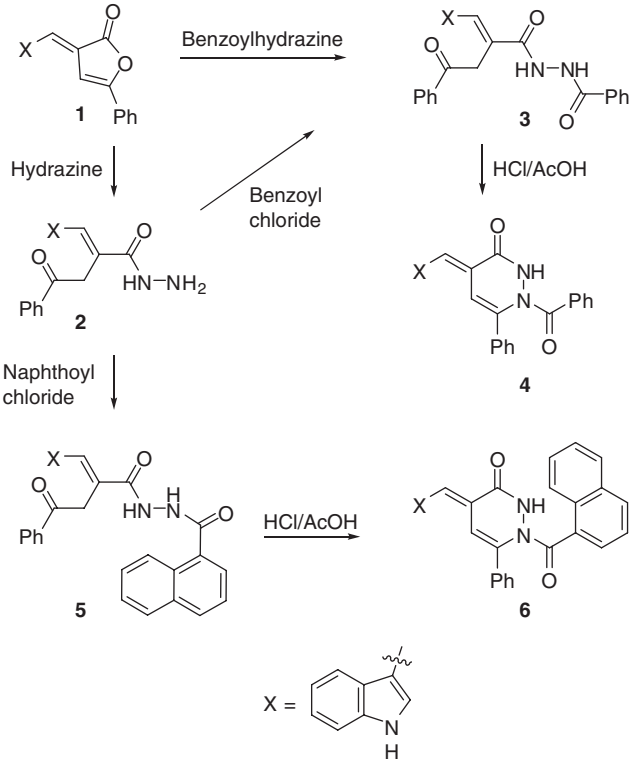
2(3*H*)-Furanones are key starting materials for the construction of many heterocyclic systems [1–16]. The key step in these transformations is the formation of the acid hydrazides, which are formed by the action of hydrazine hydrate on the furanones.

Indole-substituted compounds are common in nature [17]; one of the most important and simple derivatives is the amino acid tryptophan. Pyridazinones have been reported to possess antimicrobial [18], analgesic [19], anti-inflammatory [20], antidiabetic [21], herbicidal [22], antihypertensive [23], anticancer [24], antifungal [25], and other pharmacological properties [26]. Compounds containing 1,3,4-oxadiazole moiety have a broad biological spectrum. Two examples of compounds currently used in clinical medicine are raltegravir, an antiretroviral drug [27], and zibotentan, an anticancer agent [28]. 1,2,4-Triazoles are broad-spectrum antifungal agents used as pesticides and pharmaceuticals. They inhibit the biosynthesis of ergosterol, which is an essential component of fungal membranes [29, 30].

These reported diverse biological activities prompted us to attempt the conversion of furanone **1** into pyridazinones, 1,3,4-oxadiazoles, and 1,2,4-triazoles, all bearing an indolyl moiety. Some of the obtained products were evaluated for their antimicrobial activity.

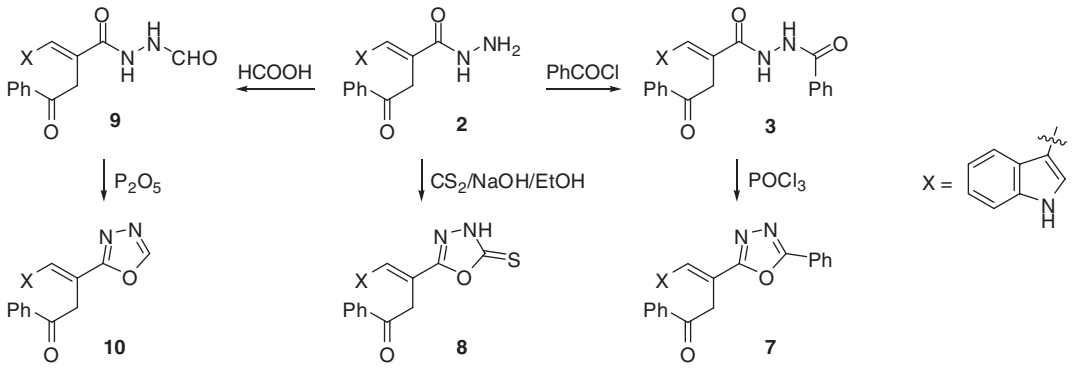
Results and discussion

The 2(3*H*)-furanone **1** has previously been prepared by one of us [3]. Hydrazide **2** has previously been prepared [4] via treating furanone **1** with hydrazine hydrate. In this work, pyridazinone **4** was synthesized by ring closure of benzohydrazide **3**, which was obtained by the reaction of



Scheme 1 Synthesis of pyridazinone derivatives.

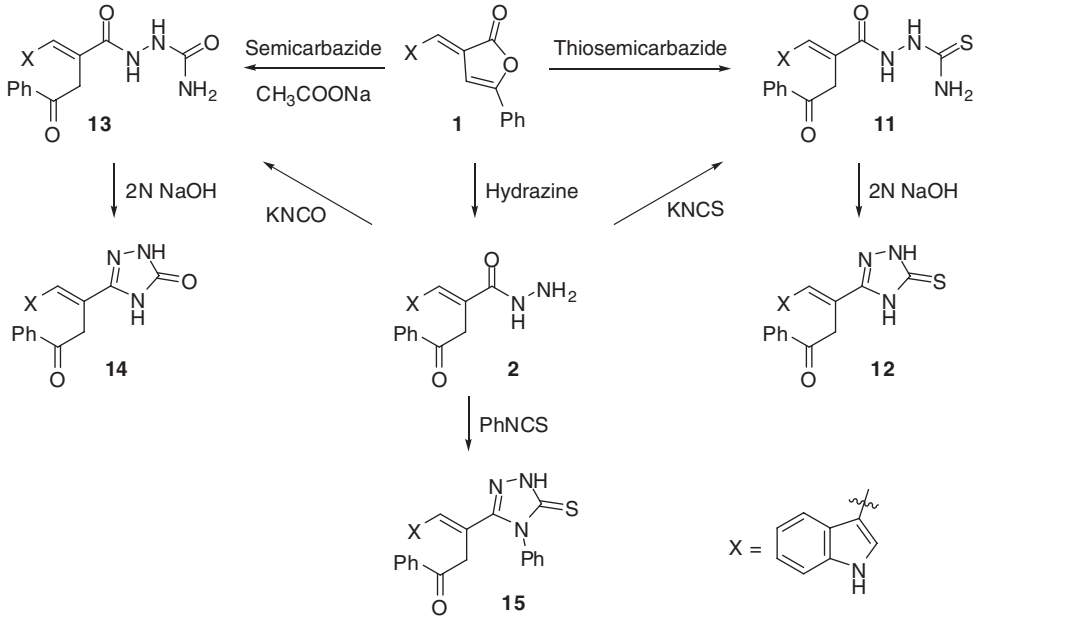
***Corresponding author: Abdelaal A. Abdalha,** Faculty of Science, Chemistry Department, Ain Shams University, Abassia, Cairo 11566, Egypt; and Chemistry Department, Tabuk University, Tabuk, KSA, e-mail: abdoelaal@yahoo.com
Wael S.I. Abou-Elmagd and Ahmed K. EL-Ziaty: Faculty of Science, Chemistry Department, Ain Shams University, Abassia, Cairo 11566, Egypt



Scheme 2 Synthesis of 1,3,4-oxadiazole derivatives.

acid hydrazide **2** with benzoyl chloride. The structure of **3** was supported by comparison with an authentic sample prepared by the treatment of furanone **1** with benzoyl hydrazine. The treatment of hydrazide **2** with naphthoyl chloride afforded naphthohydrazide derivative **5**. Ring closure of **5** by using HCl/AcOH (1:1) mixture afforded *N*-napthopyridazinone derivative **6** (Scheme 1). The structures of **3–6** are in full agreement with their analytical and spectral data.

The treatment of benzohydrazide derivative **3** with phosphorus oxychloride yielded 1,3,4-oxadiazole derivative **7**. Oxadiazolethione derivative **8** was obtained when hydrazide **2** was allowed to react with carbon disulfide in refluxing alcoholic sodium hydroxide. By contrast, the treatment of hydrazide **2** with formic acid under reflux for 10 h yielded *N*-formyl derivative **9**, which was easily cyclized through dehydration by heating with phosphorus pentoxide in dry toluene to give 1,3,4-oxadiazole derivative **10** (Scheme 2). The structures of compounds **7–10** were elucidated from their analytical and spectroscopic data. The treatment of hydrazide **2** with potassium isothiocyanate afforded thiosemicarbazide derivative **11**, which was also formed by the reaction of furanone **1** with thiosemicarbazide. Ring closure of **11** in 2N NaOH yielded triazolethione derivative **12**. Semicarbazide derivative **13** was also prepared by the reaction of hydrazide **2** with potassium isocyanate and/or treatment of furanone **1** with semicarbazide hydrochloride/sodium acetate mixture. Triazolone derivative **14** was prepared by ring closure of semicarbazide derivative **13** using 2N NaOH. By contrast,



Scheme 3 Synthesis of 1,2,4-triazole derivatives.

hydrazide **2** was allowed to react with phenyl isothiocyanate in sodium hydroxide (10%) followed by acidification to yield 4-phenyltriazolethione derivative **15** (Scheme 3). The structures of compounds **11–15** were confirmed by the analysis of the analytical and spectroscopic data.

The synthesized compounds were evaluated for their *in vitro* antimicrobial activity using four types of gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, and *Kocuria rhizophila*), two types of gram-negative bacteria (*Salmonella typhimurium* and *Escherichia coli*), and two fungus (yeast *Candida albicans* and mould *Aspergillus niger*); novobiocin, chloramphenicol, and nystatin were used as standard drugs for antibacterial and antifungal activities (Tables 1–3). The results

Table 1 Antibacterial and antifungal activities (as inhibition zone in mm diameter).

Compound	*Staphylococcus aureus*	*Kocuria rhizophila*	*Salmonella typhimurium*	*Escherichia coli*	*Candida albicans*	*Aspergillus niger*
1	20	15	11	11	12	0
4	22	24	14	15	15	0
11	20	19	16	12	13	0
13	17	11	13	10	0	0
14	21	20	14	13	0	0
12	0	0	0	0	13	13
15	0	0	0	0	14	15
Novobiocin	23	22	10	11	0	0
Chloramphenicol	23	21	17	17	0	0
Nystatin	0	0	0	0	14	0

Table 2 MIC (μg/mL) for the active compounds.

Compound	*Staphylococcus aureus*	*Kocuria rhizophila*	*Salmonella typhimurium*	*Escherichia coli*	*Candida albicans*
1	30	25	30	50	60
4	0	50	60	60	50
11	25	30	25	30	25
13	50	50	60	70	0
14	30	30	30	25	0
12	0	0	0	0	60
15	0	0	0	0	30
Novobiocin	30	25	60	50	0
Chloramphenicol	30	25	30	30	0
Nystatin	0	0	0	0	40

Table 3 Minimum bactericidal concentration (MBC, μg/mL) for active compounds.

Compound	*Staphylococcus aureus*	*Kocuria rhizophila*	*Salmonella typhimurium*	*Escherichia coli*	*Candida albicans*
1	80	70	80	70	110
4	0	70	100	110	70
11	50	70	90	130	50
13	50	80	100	100	0
14	60	50	100	50	0
12	0	0	0	0	120
15	0	0	0	0	60
Novobiocin	50	50	100	100	0
Chloramphenicol	40	40	50	50	0
Nystatin	0	0	0	0	50

revealed that the majority of the synthesized compounds show varying degrees of inhibition against the tested microorganisms. Only pyridazinones and triazoles show significant antimicrobial activities. More specifically, compounds **1**, **4**, and **11–15** exhibit high antibacterial and antifungal activities compared with the standard drugs, whereas compounds **2**, **6–8**, and **10** exhibit no antimicrobial activity.

Conclusion

A series of novel pyridazinones,1,3,4-oxadizole, and 1,2,4-triazole derivatives has been synthesized using a facile strategy and screened for antimicrobial activities. Some of the prepared compounds exhibit high antibacterial and antifungal activities compared with the standard drugs.

Experimental

Uncorrected melting points were measured on a Gallen Kamp electric melting point apparatus. Infrared spectra were recorded using potassium bromide disks on FTIR Thermo Electron Nicolet 7600 (USA) infrared spectrometer at the central laboratory of Faculty of Science, Ain Shams University. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were measured in DMSO-d_6 on a Varian plus instrument. Mass spectra were recorded on a Shimadzu GC-MS QP-1000EX mass spectrometer operating at 70 eV at the Micro Analytical Center of Cairo University. The progress of all reactions was monitored by thin layer chromatography using Merck Kiesel gel 60 F_{254} aluminum-backed plates. The spots were developed using a UV lamp.

Antimicrobial activity was conducted at El-Rashidi Elmizan Confectionery Company, 2nd industrial zone, 6th of October City, Cairo, Egypt, and Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University.

Synthesis of *N*-[2-((1*H*-indol-3-yl)methylene)-4-oxo-4-phenylbutanoyl]benzohydrazide (3)

Benzoyl chloride (10 mmol) was added to a solution of hydrazide **2** (10 mmol) in dry benzene (20 mL). The reaction mixture was heated under reflux for 3 h. The solvent was distilled under reduced pressure, and the deposited solid was filtered, washed several times with cold water, dried, and then crystallized from ethanol to give compound **3**. The same product **3** was obtained by heating a solution of furanone **1** (10 mmol) in ethanol (20 mL) with benzoyl hydrazine (10 mmol) under reflux for 2 h. The solvent was evaporated, and the solid residue was filtered, dried, and then crystallized from ethanol to give compound **3** in 60% yield as colorless crystals; mp 230–231°C; IR (ν_{max}, cm^{-1}): 3321, 3255, 3195 (NH), 1692, 1658 (C=O); ^{1}HNMR: δ 3.15 (d, 1H, *J* = 7.2 Hz), 3.42 (d, 1H, *J* = 7.2 Hz), 6.69–7.59 (m, 16H), 8.92 (s, 1H), 11.78 (br s, 2H); ^{13}C NMR: δ 38.8, 111.1, 111.9, 119.7, 120.1, 121.9, 122.2, 127.5, 127.9, 128.3, 128.7, 129.1, 130.8, 132.3, 133.2, 134.9, 135.2, 136.1, 138.3, 164.9, 165.7, 194.7; MS *m*/*z* (%): 423 (M$^+$, 15), 330 (100), 299 (27), 271 (29), 167 (32), 104 (44), 77 (48). Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.98; H, 4.93; N, 9.73.

Synthesis of *N*-[2-((1*H*-indol-3-yl) methylene)-4-oxo-4-phenylbutanoyl]naphthohydrazide (5)

Naphthoyl chloride (10 mmol) was added to a solution of hydrazide **2** (10 mmol) in dry benzene (20 mL). The reaction mixture was heated under reflux for 3 h. The solvent was distilled under reduced pressure, and the deposited solid was filtered, washed several times with cold water, dried, and then recrystallized from ethanol to give compound **5** in 65% yield as colorless crystals; mp 240–242°C; IR (ν_{max}, cm^{-1}): 3295, 3215, 3120 (NH), 1692, 1645 (C=O); ^{1}HNMR: δ 3.19 (d, 1H, *J* = 7.2 Hz), 3.22 (d, 1H, *J* = 7.2 Hz), 6.55–8.17 (m, 18H), 8.86 (s, 1H), 11.21 (br s, 2H,); ^{13}C NMR: δ 39.7, 110.6, 111.7, 119.0, 120.2, 120.5, 122.5, 126.1, 127.3, 127.4, 128.5, 128.8, 129.5, 130.3, 130.9, 131.8, 132.3, 133.7, 134.1, 134.4, 134.7, 135.2, 135.5, 136.8, 138.5, 165.7, 166.9, 194.3. MS, *m*/*z* (%): 473 (M$^+$, 18), 371 (21), 339 (22), 177 (22), 99 (27), 69 (28), 57 (100). Anal. Calcd for $C_{30}H_{23}N_3O_3$: C, 76.09; H, 4.90; N, 8.87. Found: C, 76.28; H, 4.95; N, 9.01.

General method for ring closure of benzohydrazides 3 and 5 using HCl/AcOH

A solution of **3** or **5** (1 g) in a mixture of HCl/AcOH, 1:1 (30 mL), was heated under reflux for 1 h and then cooled. The resultant solid was filtered, washed with water, and crystallized from ethanol to give the respective product **4** or **6**.

4-[(1*H*-Indol-3-yl)methylene]-1-benzoyl-6-phenyl-1,2-dihydropyridazin-3(4*H*)-one (4) This compound was obtained in 80% yield as colorless crystals; mp 136–138°C; IR (ν_{max}, cm^{-1}): 3297, 3115 (NH), 1667, 1650 (C=O); ^{1}H NMR: δ 6.20 (s, 1H), 6.50–8.59 (m, 16H), 8.90 (s, 1H), 10.11 (br s, 1H); ^{13}C NMR: δ 84.3, 110.7, 112.4, 119.6, 121.4, 122.2, 126.5, 126.9, 127.9, 128.1, 128.7, 128.9, 131.1, 132.3, 133.9, 134.4, 135.6, 135.9, 136.8, 139.7, 149.4, 169.9; MS *m*/*z* (%): 405 (M$^+$, 20), 382 (18), 330 (100), 299 (27), 286 (21), 271 (29), 155 (33), 104 (44), 77 (45), 59 (26). Anal. Calcd for $C_{26}H_{19}N_3O_2$: C, 77.02; H, 4.72; N, 10.36. Found: C, 77.17; H, 4.55; N, 10.78.

4-((1*H*-Indol-3-yl)methylene)-1-(1-naphthoyl)-6-phenyl-1,2-dihydropyridazin-3(4*H*)-one (6) This compound was obtained in 70% yield as colorless crystals; mp 163–165°C; IR (ν_{max}, cm^{-1}): 3301, 3212 (NH), 1662, 1653 (C=O); ^{1}H NMR: δ 7.17 (s, 1H), 7.20–8.43 (m, 18H), 8.82 (s, 1H), 10.21 (br s, 1H); ^{13}C NMR: δ 80.7, 110.6, 111.5, 119.6, 120.3, 122.2, 124.5, 126.1, 126.3, 126.5, 126.9, 127.9, 128.3, 128.5, 128.7, 128.9, 130.3, 130.9, 132.3, 133.5, 133.9, 134.3, 135.1, 135.9, 139.4, 139.9, 149.6, 169.7; MS *m*/*z* (%): 455 (M$^+$, 12), 354 (20), 330 (21), 279 (20), 177 (27), 151 (21), 99 (27), 69 (28),57 (100), 55 (38). Anal. Calcd for $C_{30}H_{21}N_3O_2$ (455): C, 79.10; H, 4.65; N, 9.22. Found: C, 79.23; H, 4.39; N, 9.40.

Synthesis of 4-(1*H*-indol-3-yl)-1-phenyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)but-3-en-1-one (7)

Phosphorus oxychloride (10 mL) was added dropwise to 1 g of diaroylhydrazine **3**. The reaction mixture was heated under reflux for 20 min, then cooled and poured onto crushed ice. The resultant solid was filtered, washed with water, and crystallized from ethanol to give compound **7** in 40% yield as pale yellow powder; mp 178–180°C; IR (ν_{max}, cm^{-1}): 3312 (NH), 1671 (C=O); ^{1}H NMR: δ 3.15 (d, 1H, *J* = 7.0 Hz), 3.25 (d, 1H, *J* = 7.0 Hz), 7.40–8.20 (m, 16H), 8.84 (s, 1H); ^{13}C NMR: δ 43.6, 110.6, 111.3, 119.0, 120.1, 121.7, 126.3, 126.7, 127.5, 128.1, 128.3, 128.7, 129.8, 130.3, 133.2, 135.9, 136.4, 140.3, 164.3, 164.7, 193.9; MS *m*/*z* (%): 405 (M^+, 67), 171 (28), 145 (20), 129 (100), 117 (14), 105 (71), 88 (41), 76 (55). Anal. Calcd for $C_{26}H_{19}N_3O_2$: C, 77.02; H, 4.72; N, 10.36. Found: C, 77.37; H, 4.78; N, 10.73.

Synthesis of 4-(1*H*-indol-3-yl)-1-phenyl-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)but-3-en-1-one (8)

Carbon disulfide (10 mL) was added to a solution of hydrazide **2** (10 mmol) in 10% alcoholic NaOH (3 g NaOH in 30 mL ethanol) whereby the reaction mixture became brown. The mixture was heated under reflux for 2 h, then cooled and poured onto ice-cold water. Acidification with concentrated HCl gave a yellow precipitate, which was filtered and crystallized from ethanol to give compound **8** in 80% yield as yellow powder; mp 218–220°C; IR (ν_{max}, cm^{-1}): 3273, (NH), 1666 (C=O); ^{1}H NMR: δ 3.35 (d, 1H, *J* = 7.2 Hz), 3.93 (d, 1H, *J* = 7.2 Hz), 6.94–7.66 (m, 11H), 9.13 (s, 1H), 13.12 (br s, 1H); ^{13}C NMR: δ 35.4, 110.9, 113.4, 119.6, 120.3, 122.2, 126.5, 128.7, 128.9, 131.1, 133.2, 134.1, 134.4, 135.6, 136.4, 160.1, 165.6, 196.5; MS *m*/*z* (%): 361 (M^+, 76), 259 (16), 219 (23), 173 (16), 105 (36), 76 (45), 51 (100). Anal. Calcd for $C_{20}H_{15}N_3O_2S$ (361): C, 66.46; H, 4.18; N, 11.63; S, 8.87. Found: C, 66.62; H, 4.23; N, 11.50; S, 8.65.

Synthesis of 2-[(1*H*-indol-3-yl)methylene]-*N*-formyl-4-oxo-4-phenyl butane hydrazide (9)

A solution of **2** (1 g) in formic acid (10 mL) was heated under reflux. The deposited solid during heating after 7 h was filtered, washed several times with water, dried, and then recrystallized from dioxane to give compound **9** in 50% yield as colorless crystals; mp 256–257°C; IR (ν_{max}, cm^{-1}): 3320, 3255, 3170 (NH), 1710, 1672, 1650 (C=O); ^{1}H NMR: δ 3.18 (d, 1H, *J* = 7.0 Hz), 3.25 (d, 1H, *J* = 7.0 Hz), 6.89–8.45 (m, 11H), 8.60 (s, 1H), 9.05 (s, 1H), 10.1 (br s, 1H), 10.5 (s, 1H); ^{13}C NMR: δ 39.8, 110.9, 111.9, 119.7, 120.1, 122.2, 126.5, 127.9, 128.3, 131.1, 133.8, 135.3, 135.7, 136.9, 138.3, 165.1, 166.7, 195.1; MS *m*/*z* (%): 347 (M^+, 21), 204 (56), 173 (85), 145 (100), 117 (22), 105 (76), 90 (87), 76 (50), 55 (45). Anal. Calcd For $C_{20}H_{17}N_3O_3$ (347): C, 69.15; H, 4.93; N, 12.10. Found: C, 69.47; H, 4.73; N, 12.37.

Synthesis of 4-(1*H*-indol-3-yl)-3-(1,3,4-oxadiazol-2-yl)-1-phenyl but-3-en-1-one (10)

A mixture of compound **9** (1 g) and phosphorus pentoxide (1 g) in dry toluene (20 mL) was heated under reflux for 3 h. The deposited solid was filtered, washed several times with water, dried, and crystallized from ethanol to give compound **10** in 60% yield as pale yellow powder; mp 230–233°C; IR (υ_{max}, cm^{-1}): 3242 (NH), 1655 (CO); ^{1}HNMR: δ 3.10 (d, 1H, *J* = 7.0 Hz), 3.15 (d, 1H, *J* = 7.0 Hz), 7.02–8.14 (m, 12H), 8.93 (s, 1H); ^{13}C NMR: δ 42.3, 110.6, 111.3, 119.0, 120.1, 126.3, 126.7, 127.5, 128.7, 129.8, 130.3, 133.2, 135.9, 140.3, 155.9, 157.2, 194.1; MS *m*/*z* (%): 329 (M^+, 56), 171 (27), 145 (45), 129 (100), 117 (64), 105 (30), 88 (41). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.77; H, 4.43; N, 12.57.

Synthesis of thiosemicarbazide 11 and semicarbazide 13

A solution of potassium thiocyanate or potassium cyanate (12 mmol) in water (10 mL) was added dropwise with stirring at 0°C to a solution of hydrazide **2** (10 mmol) in AcOH/H_2O (1:1 by volume) mixture. The reaction mixture was stirred at room temperature for 3 h. The product obtained was filtered, washed thoroughly with water, and finally recrystallized from ethanol/dioxane mixture to give thiosemicarbazide **11** (from thiocyanate) and semicarbazide **13** (from cyanate).

The same product **11** was also obtained by heating under reflux a solution of 2(3*H*)-furanone **1** (10 mmol) in ethanol (30 mL) with thiosemicarbazide (10 mmol) for 1 h. Heating **1** (10 mmol) with a mixture of semicarbazide hydrochloride (10 mmol) and anhydrous sodium acetate (10 mmol) for 1 h gave product **13**. The solid obtained was filtered, washed thoroughly with water, and recrystallized to give compounds **11** and **13**, respectively.

1-[2-((1*H*-Indol-3-yl)methylene)-4-oxo-4-phenylbutanoyl]thiosemicarbazide (11) This compound was obtained in 50% yield as colorless crystals; mp 159–160°C; IR (υ_{max}, cm^{-1}): 3325, 3216, 3195, 3117 (NH), 1677, 1640 (C=O), 1252 (C=S); ^{1}HNMR: δ 3.22 (s, 2H), 6.99–7.86 (m, 11H), 8.63 (s, 1H), 11.40 (br s, 1H), 11.63 (br s, 2H), 12.09 (br s, 1H); ^{13}C NMR: δ 39.3, 110.7, 111.3, 119.1, 120.3, 122.2, 126.3, 128.3, 128.9, 130.3, 133.5, 135.3, 135.7, 136.9, 138.3, 165.3, 182.5, 194.3; MS *m*/*z* (%): 378 (M^+, 11), 181 (78), 153 (32), 148 (38), 120 (84), 106 (38), 93 (100), 77 (88), 66 (47). Anal. Calcd for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80; S, 8.47. Found: C, 64.12; H, 4.53; N, 15.03; S, 8.87.

1-[2-((1*H*-indol-3-yl)methylene)-4-oxo-4-phenylbutanoyl]semicarbazide (13) This compound was obtained in 56% yield as colorless crystals; mp 200–202°C; IR (υ_{max}, cm^{-1}): 3320, 3212, 3170, 3110 (NH), 1677, 1630 (C=O); ^{1}H NMR: δ 3.20 (s, 2H), 7.03–7.97 (m, 11H), 8.52 (s, 1H), 11.97 (br.s, 2H), 12.86 (br s, 2H); ^{13}C NMR: δ 38.7, 110.3, 111.1, 119.3, 120.6, 121.7, 126.1, 127.9, 128.2, 130.1, 134.9, 135.1, 136.3, 138.0, 158.1, 165.1, 193.7; MS, *m*/*z* (%): 362 (M^+, 9), 186 (42), 257 (21), 154 (35), 127 (24), 117 (34), 104 (53), 93 (46), 77 (100), 65 (38), 51 (46). Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.07; H, 4.92; N, 15.10.

Synthesis of triazol-5-thione 12 and triazol-5-one 14

A solution of 2N NaOH (40 mL) was added to thiosemicarbazide **11** (10 mmol) or semicarbazide **13** (10 mmol). The reaction mixture was heated under reflux for 2 h, filtered while hot, acidified with ice-cold HCl, and diluted with 100 mL of water. The solid obtained was filtered, washed with water, and crystallized from ethanol to give triazol-5-thione **12** or triazol-5-one **14**, respectively.

3-(1-(1*H*-Indol-3-yl)-4-oxo-4-phenylbut-1-en-2-yl)-5-thioxo-4,5-dihydro-1,2,4-triazole (12) This compound was obtained in 70%

yield as colorless crystals; mp 204–206°C; IR (υ_{max}, cm^{-1}): 3302, 3213, 3125 (NH), 1663 (C=O); ^{1}HNMR: δ 3.23 (s, 2H), 6.75–8.02 (m, 11H), 9.30 (s, 1H), 12.98 (br s, 2H);^{13}C NMR: δ 35.3, 110.7, 111.1, 119.7, 120.1, 121.9, 126.2, 128.3, 128.7, 130.8, 132.3, 133.2, 134.9, 135.2, 136.9, 156.1, 189, 194.3; MS *m*/*z* (%): 360 (M^+, 35), 310 (49), 293 (51), 187 (51), 117 (52), 84 (58), 58 (100). Anal. Calcd for $C_{20}H_{16}N_4OS$: C, 66.65; H, 4.47; N, 15.54; S, 8.90. Found: C, 66.92; H, 4.32; N, 15.13; S, 8.77.

3-(1-(1*H*-Indol-3-yl)-4-oxo-4-phenylbut-1-en-2-yl)-5-oxo-4,5-dihydro-1,2,4–triazole (14) This compound was obtained in 74% yield as colorless crystals; mp 234–237°C; IR (υ_{max}, cm^{-1}): 3302, 3218, 3184 (NH), 1665, 1634 (C=O); ^{1}H NMR: δ 3.28 (s, 2H), 6.97–8.03 (m, 11H), 9.23 (s, 1H), 12.53 (br s, 2H); ^{13}C NMR: δ 33.6, 110.3, 111.5, 119.1, 119.9, 121.7, 126.3, 128.3, 128.7, 130.8, 132.8, 133.1, 134.9, 135.5, 136.8, 156.3, 163, 194.7; MS *m*/*z* (%): 344 (M^+,7), 285 (69), 257 (77), 242 (44), 154 (35), 127 (41), 104 (37), 91 (28), 77 (100), 65 (88), 51 (35). Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.47; H, 4.42; N, 15.98.

Synthesis of 3-(1-(1*H*-indol-3-yl)-4-oxo-4-phenylbut-1-en-2-yl)-4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazole (15)

A mixture of **2** (10 mmol) and phenyl isothiocyanate (1.6 mL, 10 mmol) in (10%) sodium hydroxide (20 mL) was heated under reflux for 3 h, then cooled and acidified with cold dilute hydrochloric acid. The deposited solid was filtered, washed several times with cold water, dried, and crystallized from dioxane to give compound **15** in 55% yield as colorless crystals; mp 215–217°C; IR (υ_{max}, cm^{-1}): 3312, 3214, 3184 (NH), 1677 (C=O); ^{1}H NMR: δ 3.32 (s, 2H), 6.62–7.99 (m, 16H), 9.08 (s, 1H), 11.35 (br s, 1H); ^{13}C NMR: δ 43.1, 111.3, 111.8, 119.6, 120.4, 122.2, 124.7, 126.5, 128.5, 128.7, 129.4, 130.1, 132.3, 133.2, 133.9, 134.4, 135.9, 136.6, 136.8, 155.9, 160.7, 194.5; MS *m*/*z* (%): 436 (M^+, 18), 362 (16), 308 (15), 279 (18), 252 (19), 169 (16), 151 (22), 94 (17), 78 (18), 66 (20), 58 (100). Anal. Calcd for $C_{26}H_{20}N_4OS$ (436): C, 71.54; H, 4.62; N, 12.83; S, 7.35. Found: C, 70.92; H, 4.93; N, 12.65; S, 7.67.

Biological assays

All microorganisms were kindly provided from the culture collection of the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University. Malt extract agar was used as a medium for fungal isolates, and nutrient agar medium was used for bacterial growth. Each medium was prepared by dissolving the solid ingredients in 1 L of cold distilled water and then by heating to 60–70°C with stirring. Media were sterilized by autoclaving at 121°C (1.5 atm) for 15–20 min.

By using a diffusion agar technique, antifungal and antibacterial activities were measured as the diameter of the inhibition zone. Inhibition zones developed due to active ingredients were measured after 24–48 h of incubation time. Minimum inhibitory concentration (MIC) was determined by a serial dilution technique [31, 32]. To determine the minimum bactericidal concentration (MBC), the dilution representing the MIC and at least two of the more concentrated test product dilutions were plated and enumerated to determine viable colony-forming unit (CFU) per milliliter. The MBC is the lowest concentration that demonstrates a predetermined reduction (such as 99.9%) in CFU per milliliter when compared with the MIC dilution [31, 32].

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